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<p>(21) International Application Number: PCT/GB96/00181</p> <p>(22) International Filing Date: 29 January 1996 (29.01.96)</p> <p>(30) Priority Data: 9501579.8 27 January 1995 (27.01.95) GB</p> <p>(71) Applicant (for all designated States except US): LOUGHBOROUGH UNIVERSITY OF TECHNOLOGY [GB/GB]; Ashby Road, Loughborough, Leicestershire LE11 3TU (GB).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): WILKINSON, Francis [GB/GB]; 22 Fairmount Drive, Loughborough, Leicestershire LE11 3JR (GB). MANDLEY, David, John [GB/GB]; 1 Ulley View, Aughton, Sheffield, South Yorkshire S31 0XX (GB).</p> <p>(74) Agents: McNEIGHT, David, Leslie et al.; McNeight &amp; Lawrence, Regent House, Heaton Lane, Stockport, Cheshire SK4 1BS (GB).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: ENHANCEMENT OF ACTIVATION FOR "BIOLOGICAL" TISSUE ADHESIVES, BONDING AGENTS AND SEALANTS USING "COLOUR CHANGE" CHROMOPHORES</p> <p>(57) Abstract</p> <p>There is disclosed a method for effecting a reaction by irradiating a substance which absorbs the radiant energy until the reaction is complete and the absorbency of the material changes so as to reduce or cease absorption of further radiant energy.</p>		

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**ENHANCEMENT OF ACTIVATION FOR 'BIOLOGICAL' TISSUE ADHESIVES,  
BONDING AGENTS AND SEALANTS USING "COLOUR CHANGE" CHROMOPHORES.**

This invention relates to particularly but not exclusively, the effective "setting" or "curing" of an adhesive and more particularly still to effecting the setting of a tissue bonding adhesive or sealant.

WO 92/02238 discloses compositions of various predominantly 'biological' adhesives to bond separated tissues together or to coat tissues or prosthetic material, to enhance strength and water-tightness upon the application of energy and particularly compositions activated by radiation not least laser radiation. Thus a stronger bio-compatible bond or coating is formed. The formation of such a bond or coating being referred to generally hereinafter as "setting" the adhesive.

Such adhesives may be used instead of suturing and stapling for example in surgical procedures for repair or the creation of anastomoses.

The application of a suitable biocompatible adhesive offers many advantages to patient and surgeon alike. It avoids penetration of tissues by needles, as well as immediately sealing the treated tissue. It would prevent or minimise foreign body reaction and scarring. Such a suitable substance could be quicker to apply and may well be more accurate than standard suturing - particularly where small vessels or structures are concerned. There is also the potential advantage, that if the "setting"

energy is sufficiently low, analgesia may not be required. There are many different applications for such a material, not only for bonding anastomoses but also for dressings, haemostats and sealants.

The 'ideal' adhesive, would be non-toxic and biocompatible, strong and supple. It would not unduly swell after setting, would be user-friendly to apply and would be easy to sterilise and prepare.

WO 92/02238 refers to prior art fibrin adhesives as well as other multi-component adhesives. It suggests essentially a two main component adhesive comprising natural or synthetic peptides. These proteins/peptides may be modified enzymatically, chemically or otherwise. They may thus be shortened/cleaved, cross-linked, oxidised or hydrolysed, as a whole or be derivatives of subunits thereof. The original protein with or without modification may be added to by fibrous or structural proteins - for example synthetic or natural collagen, elastin keratin, fibrin, fibronectin and others. Examples of serum proteins, albumin, various globulins and others are given. All these proteins or their derivatives or additives act as the first component constituents.

The second component is said to be generally selected from constituents supporting the first component, such as forming a matrix, gel or sol therewith, usually natural or synthetic proteoglycans, glycoproteins, saccharides, gelatins or

polyalcohols and others. Again these components may be modified. Mucopolysaccharides, typically glysoaminoglycans including hyaluronic acid its salts, chondroitin sulphate, heparan sulphate may be incorporated.

Other additives may be used, examples being polyvalent cations eg. calcium. These may act as bonding enhancers. Additional components such as pH modifiers, citric acid, ascorbic acid may be used together with preservatives, surfactants and EDTA.

The composition of these ingredients and others may be modified in concentration and variations in the molecular weight of constituents also altered to suit the application and the purpose. Viscosity may be changed from liquid to a viscous gel. Additions of non-Newtonian fluids may offer altered physical properties such as pseudoplasticity which may change a relatively viscous material to a liquid under shear forces eg. by syringe injection.

In some circumstances the combination of peptides and other previously mentioned constituents may spontaneously set, thus for example uniting arterial edges to form a 'weld'. In other cases it is necessary to activate the composition with energy and/or photons. Whilst a variety of energy/photon sources have been proposed, most preferable are lasers, including those in the visible or IR ranges, a number of such are mentioned including Nd:YAG and Argon Lasers. UV sources may also be used.

A major advantage of lasers is the precise application of laser energy to selected areas, made possible by the coherent nature

and hence narrow beam feature of laser emission. Importantly the beam can be very easily and conveniently directed even to difficult access surgical sites by using optical fibre arrangements.

The use of endogenous or exogenous chromophores significantly enhance laser use. Incorporating suitable chromophores into the adhesive has several advantages. The chromophores, of which many have been quoted and used, selectively absorb the laser light energy and convert that energy to thermal energy where it has been applied. The chromophore is chosen for any specific wavelength. The heat generated then sets the adhesive. Thus chromophores enhance accuracy and distribute setting energy. Suitably chosen chromophores will also help reach setting temperatures quickly, thus reducing the time factor for laser application and importantly the overall energy requirements. On account of the selectivity of the chromophores for any given wavelength and the accuracy of such a system, thermal injury to tissue is significantly reduced or avoided.

The benefits of the combination of chromophores and laser may be further enhanced by partially setting the adhesive before ultimate application. This further reduces the final setting energy levels and has obvious clinical advantages.

There are a few major potential problems using lasers for bonding or activating adhesives or indeed using other energy sources. The time taken for setting or bonding is usually a few seconds. Exposure of just a few more seconds may damage the underlying

tissue being treated or other surrounding tissue. The operator will usually see a faint glow when the appropriate setting temperature has been obtained. However this is unreliable and indeed may be difficult in taxing surgical application or conditions. It is thus relatively easy for the operator to either under-irradiate or over-irradiate.

This invention describes the use of "colour change" chromophores which will demonstrate to the operator that the suitable end point has been reached. More importantly, the invention gives further protection and confidence to the operator by comprising of a method, effecting such a reaction by irradiating a substance which absorbs the radiant energy until the reaction is sufficiently complete and the absorbance of the material changes so as to significantly reduce or cease absorption of further energy. Thus not only has the end point been clarified, but also safety has been enhanced by reducing the possibility of further potentially damaging energy being absorbed.

The reaction may comprise the setting of an adhesive such as a composition which bonds to living or other tissue or other materials. In the living tissue situation the components may be modified to enhance structural heating and to encourage cellular ingrowth.

The substance with or without additional components may comprise of a chromophore or group of chromophores which changes per se following irradiation or which reacts with another substance eg.

ascorbic acid, to change in the conditions brought about by irradiation.

The method may be used to effect setting of an adhesive or potential adhesive applied to living or other tissue, in which the adhesive is irradiated with radiation which is poorly absorbed by the tissue but well absorbed by the adhesive until it changes colour, which prevents undesirable effects as a consequence of over-irradiation.

The substance may be irradiated by laser light to effect the reaction, which may be in the IR, visible or UV region of the spectrum. The choice of wavelength and chromophore may be altered for different applications.

The Argon laser at 488 and 514 nm is suitable for many applications. Laser power output may be altered. 0.15W-0.3W being commonly used. Power may be reduced to 0.05W in thermally pre-treated adhesives, eg. pre-treatment in which the material is incubated to approximately 70% of setting temperature for 1-2 hours.

Irradiation time of some 10 seconds are commonly applied at 0.2W for small diameter anastomoses using the Argon laser, but may be varied. Preferably the chromophore's absorption should reduce to a level at which the same laser power could be applied as long again or twice as long again without giving rise to further thermal damage.



Laser spot sizes may also be altered for different application. Frequently a spot size of 1mm diameter has been used. Power density may also be varied. Commonly  $10\text{W}/\text{cm}^2$  are used.

This invention also comprises an additive for a tissue adhesive adapted to absorb radiation to set the adhesive and when the adhesive is set, to change so as to reduce or cease absorption of radiation.

The additive may comprise a radiation absorbing substance convertible on irradiation to give a reduced absorption or non-absorbing substance.

Thus the additive may comprise a chromophore and a reactant therefore adapted to effect the conversion - for example a suitable red/orange coloured dye having an absorption maximum in the 400 - 520 nm region for use with an Argon Laser.

Several examples of such a dye are available, such as fuchsin, phloxin, erythrosin and eosin. They may be presented dissolved in say Ringers Solution and may have a concentration between  $0.1\text{ mol}/\text{dm}^3$  and  $0.05\text{ mol}/\text{dm}^3$ , but may be varied. Other solutions may be used as illustrated in later examples.

The additive may comprise a reducing agent as a conversion effecting reagent. The reducing agent may comprise for example, ascorbic acid which may be present at  $0.11\text{ mol}/\text{dm}^3$  concentration or EDTA which may be present at  $0.2\text{ mol}/\text{dm}^3$  concentration.

The invention also comprises a tissue bonding adhesive containing the additives or similar appropriate additives described above. The adhesive may comprise albumin, which may be in solution, eg. in Ringers Solution between 10 and 40% w/w or other appropriate solutions.

Adhesives containing additives and modifications according to the invention may be used in a variety of circumstances and be presented, applied and prepared in many ways. In addition to vascular anastomoses, gut, ureteric and urethral applications may be used. Tissues of all descriptions, including liver and kidney may be repaired both by application to lacerated areas as well as by closing haemorrhagic sites. They may also be applied directly or endoscopically to areas of resected or damaged lung parenchyma. They may also be applied to seal drainage tubes or to seal areas after tube removal.

The various adhesive recipes may be coated and/or pre-treated (as required) onto patches of material, synthetic or biological or onto prostheses, such as vascular prostheses, to aid joining such prostheses to the free ends or sides of veins or arteries - for example in bypass procedures. They may also be used for sealing or coating vascular grafts.

The invention is not limited to the additives, dyes, solvents, adhesives and reagents disclosed above, nor to the use of the same for the purpose referred to. Nevertheless, it is anticipated that a very important application of the method and

the additives and adhesives will be in the area of human and veterinary surgery and that a range of adhesives and additives suitable therefore will be developed for different purposes and applications in that area.

#### EXAMPLES OF ADHESIVES CONSTITUENTS SUPPORTING THE INVENTION

These examples demonstrate the potential benefits of a colour-change chromophore which fades or changes colour and therefore alters absorption, following the setting process.

EXAMPLE 1 - NON-FADING CHROMOPHORE SOLUTION (Bovine albumin, heparan sulphate, chondroitin sulphate A and eosin Y)

##### 1. BOVINE ALBUMIN

0.4g of lyophilized powder Bovine albumin (Sigma Chemicals A2153) dissolved in 1cm<sup>3</sup> of Ringers solution.

(Small amounts of powdered bovine albumin added gradually to the stirred Ringers solution)

##### 2. CHONDROITIN SULPHATE

0.1g of chondroitin sulphate A (sodium salt) (Sigma Chemicals C 9819) dissolved in 1cm<sup>3</sup> of Ringers solution.

SAME METHOD TO DISSOLVE AS BOVINE ALBUMIN

##### 3. HEPARAN SULPHATE

To the 1cm<sup>3</sup> solution of bovine albumin prepared in stage 1, added 0.28mg of Heparan sulphate (sodium salt) (Fluka biochemicals

51541). Stirred solution slowly to ensure heparan sulphate had dissolved.

#### 4. EOSIN Y CHROMOPHORE

To the 1cm<sup>3</sup> solution of bovine albumin/heparan sulphate prepared in stages 1 and 3, added a visible light absorbing chromophore EOSIN Y. (Aldrich Chemicals 11,983-0).

Consisted of 0.01359g of Eosin Y in 1cm<sup>3</sup> bovine albumin /heparan sulphate mixture.

Concentration of Eosin Y:

$$\frac{0.01350 \times 1000}{\frac{691.88}{1}} = 0.0196 \text{ mol/dm}^3$$

SPLIT THE 1CM<sup>3</sup> SOLUTION OF BOVINE ALBUMIN/HEPARAN SULPHATE/EOSIN INTO TWO 0.5CM<sup>3</sup> FRACTIONS.

To one 0.5cm<sup>3</sup> fraction added 0.2cm<sup>3</sup> of the Chondroitin sulphate A solution prepared in stage 2.

EXAMPLE 2. - FADING CHROMOPHORE SOLUTION (Bovine albumin, heparan sulphate, chondroitin sulphate A, eosin Y and EDTA).

1. To the second 0.5cm<sup>3</sup> fraction of bovine albumin/heparan sulphate/eosin Y prepared for example 1, added 0.2cm<sup>3</sup> of the Chondroitin Sulphate A solution (stage 2 EXAMPLE 1)

PLUS

2. Ethylenediametetractic acid (EDTA) (The chemical responsible for dye fading)

Prepared a solution of EDTA (disodium salt dihydrate) (Aldrich Chemicals 25,235-2) consisting of 0.77298g of EDTA in 10cm<sup>3</sup> Ringer's solution.

Concentration of EDTA

$$\frac{0.77298 \times 1000}{372.24} = 0.20 \text{ mol/dm}^3$$

ADDED 0.1CM<sup>3</sup> OF THE 0.20mol/dm<sup>3</sup> SOLUTION PREPARED ABOVE (STAGE 2) TO 0.7CM<sup>3</sup> OF THE BOVINE ALBUMIN CHONDROITIN SULPHATE A SOLUTION.

When combined with bovine albumin/heparan sulphate/eosin y/chondroitin sulphate, the concentration of EDTA is 0.025mol/dm<sup>3</sup>

#### BURST PRESSURE RESULTS USING THESE SOLUTIONS

End to end anastomosis of porcine splenic arteries, prepared using a laser power of 0.2 watts and spot size of 1mm.

#### EXAMPLE 1 (NO DYE FADING)

138.1 250, 446.5, 219.8, 421.8, 272.7, 85.4, 89.7mmHg

#### EXAMPLE 2. (WITH DYE FADING)

495.8, 259.2, 308.6, 482.4, 403.9, 366.9, 317.6, 296.3, 291.8mmHg

Eosin Chromophore + Bovine albumin + Heparan sulphate  
+ Chondroitin sulphate, with and without EDTA (fading  
agent). BURST PRESSURES(mmHg)

0.2W

Condition	With EDTA (9)	Without EDTA (8)
Mean	358.06	240.5
Standard deviation	80.7	129.5
95% confidence limit	292.2 - 420.1	132.2 - 348.8

COMMENT : Although these were not appreciable time differences for performing the anastomoses in either group, the bursting pressures were significantly higher in the chromophore fading group. Histological examination of both groups demonstrated significant thermal injury in the group without fading chromophores and no injury or minimal thermal damage in the chromophore fading group.

This invention of a colour change chromophore, giving a clear "endpoint" for laser radiation used for setting adhesives, enhances the performance and safety of such adhesives.

**CLAIMS**

1. A method for effecting a reaction by irradiating a substance which absorbs the radiant energy until the reaction is complete and the absorbency of the material changes so as to reduce or cease absorption of further radiant energy.
2. A method according to claim 2, in which the reaction comprises the setting of an adhesive.
3. A method according to claim 2, in which the adhesive is a composition which bonds to animal tissue.
4. A method according to any one of claims 1 to 3, in which the substance comprises a chromophore which change per se on irradiation or which reacts with another substance to change in the conditions brought about by irradiation.
5. A method according to any one claims 1 to 4, used to effect setting of an adhesive applied to animal tissue in which the adhesive is irradiated with radiation which is poorly absorbed by the tissue but well absorbed by the material until it changes.
6. A method according to any one of claims 1 to 5, in which the substance is irradiated by laser light to effect the reaction.

7. A method according to claim 6, in which the laser light is in the visible spectrum.
8. A method according to claim 6, in which the laser light is in the IR spectrum.
9. An additive for an animal tissue adhesive adapted to absorb radiation to set the adhesive and when the adhesive is set to change so as to reduce or cease absorption of radiation.
10. An additive for an animal tissue adhesive comprising a radiation absorbing substance convertible on irradiation to a reduced absorbency or non-absorbent substance.
11. An additive according to claim 10, comprising a chromophore and a reactant therefor adapted to effect the conversion.
12. An additive according to claim 11 or claim 12, comprising a red/orange coloured dye.
13. An additive according to claim 12, in which the dye has an absorption maximum in the 400-520 nm region.
14. An additive according to claim 13, in which the dye comprises basic fuchsin.



15. An additive according to claim 13, in which the dye comprises philoxim.
16. An additive according to claim 13, in which the dye comprises erythrosin.
17. An additive according to claim 13, in which the dye comprises eosin.
18. An additive according to any one of claims 11 to 17, comprising a dye dissolved in Ringer solution.
19. An additive according to claim 18, with the dye in concentration between  $0.01 \text{ mol/dm}^3$  and  $0.05 \text{ mol/dm}^3$ .
20. An additive according to any one of claims 10 to 19, comprising a reducing agent as conversion effecting reagent.
21. An additive according to claim 20, in which said reducing agent is ascorbic acid.
22. An additive according to claim 21, in which said ascorbic acid is present in 0.1 - 1M concentration.
23. An additive according to claim 20, in which said reducing agent is EDTA.
24. An additive according to claim 23, in which the EDTA is present in 0.02 - 0.5M concentration.

25.       **An animal tissue bonding adhesive comprising an additive according to any one of claims 10 to 24.**
26.       **An adhesive according to claim 25, comprising albumin.**
27.       **An adhesive according to claim 26, the albumin in solution between 10 and 40% w/w.**
28.       **An adhesive according to claim 27, the albumin in Ringers solution.**

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 96/00181

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61L25/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THE JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY, vol. 103, no. 4, April 1992, pages 781-783, XP000572402 J.S. AUTERI ET AL.: "LASER ACTIVATION OF TISSUE SEALANT IN HAND-SEWN CANINE ESOPHAGEAL CLOSURE" see abstract	1-28
X	--- LASERS IN SURGERY AND MEDICINE, vol. 13, no. 5, 1993, US, pages 577-580, XP000397035 D.P. POPPAS ET AL.: "PREPARATION OF HUMAN ALBUMIN SOLDER FOR LASER TISSUE WELDING" see the whole document --- -/--	1-28

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

4 June 1996

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International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 02238 (L.S. BASS ET AL.) 20 February 1992 cited in the application see claims ---	1-28
X	JOURNAL OF CLINICAL LASER MEDICINE & SURGERY, vol. 11, no. 3, June 1993, pages 123-126, XP002004722 M.C. OZ ET AL.: "LASER-ASSISTED FIBRINOGEN BONDING OF UMBILICAL VEIN GRAFTS" see abstract ---	1-6
X	ARCHIVES OF SURGERY, vol. 125, no. 11, November 1990, pages 1452-1454, XP000572196 N. MOAZAMI ET AL.: "REINFORCEMENT OF COLONIC ANASTOMOSES WITH A LASER AND DYE-ENHANCED FIBRINOGEN" see page 1454 ---	1-6
A	PROCEEDINGS OF LASERS IN OTOLARYNGOLOGY, DERMATOLOGY, AND TISSUE WELDING, vol. 1876, January 1993, US, pages 175-179, XP002004723 M.M. JUDY ET AL.: "HEAT FREE PHOTOCHEMICAL TISSUE WELDING WITH 1,8-NAPHTHALIMIDE DYES USING VISIBLE (420 NM) LIGHT" see abstract -----	1

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PL 1/GB 96/00181

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9202238	20-02-92	US-A- 5209776	11-05-93
		US-A- 5292362	08-03-94
		AU-B- 8497991	02-03-92
		CA-A- 2087957	28-01-92
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